

Primary Liver Cancer, Other Malignancies, and Mortality Risks following Porphyrria: A Cohort Study in Denmark and Sweden

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Cancer incidence and mortality risks were evaluated in a combined cohort of patients who were hospitalized for porphyria in Denmark (1977–1989) and Sweden (1965–1983). Patients were identified by using population-based hospitalization registries. The unique individual identification numbers of 530 patients with porphyria cutanea tarda (PCT) and 296 with acute intermittent porphyria (AIP) were linked to the nationwide cancer and death registries. Among patients with both types of porphyria, the authors found small but significantly elevated risks of all cancers combined (PCT: standardized incidence ratio (SIR) = 1.7, 95% confidence interval (CI) 1.3–2.2; AIP: SIR = 1.8, 95% CI 1.1–2.8) due to pronounced excesses of primary liver cancer (PCT: SIR = 21.2, 95% CI 8.5–43.7; AIP: SIR = 70.4, 95% CI 22.7–164.3) and moderate increases in lung cancer (PCT: SIR = 2.9, 95% CI 1.5–5.2; AIP: SIR = 2.8, 95% CI 0.3–10.2). PCT patients had a significantly increased risk of mortality from liver cirrhosis (standardized mortality ratio (SMR) = 8.4, 95% CI 3.1–18.4) or chronic obstructive pulmonary disease (SMR = 3.1, 95% CI 1.1–6.7). The increased risk of primary liver cancer and the increased risk of mortality from cirrhosis of the liver are consistent with findings from previous clinical surveys, but the new observations of excess lung cancer and chronic obstructive pulmonary disease require confirmation. *Am J Epidemiol* 1999;149:1010–15.

incidence; liver cirrhosis; liver neoplasms; lung diseases, neoplasms; mortality; porphyria, acute intermittent; porphyria cutanea tarda

The porphyrias are caused by deficiencies of specific enzymes of heme biosynthesis. These disorders are sometimes inherited and are characterized by a variety of hepatic, hematologic, neurologic, and/or cutaneous manifestations (1). Classification schemes have used clinical manifestations and the primary site of heme biosynthesis regulation to distinguish erythropoietic from hepatic forms (2). The porphyrias are now categorized according to the specific enzyme deficiency. Generally, the most common subtype is porphyria cutanea tarda (PCT), which is caused by a deficiency of uroporphyrinogen decarboxylase in the liver.

Sporadic and familial forms are both manifest by cutaneous photosensitivity and liver disease (3, 4). Acute intermittent porphyria (AIP), frequent in Sweden but uncommon outside of northern Europe, is an inherited autosomal dominant disorder due to partial deficiency of porphobilinogen deaminase and is characterized by episodic attacks of abdominal pain and other neurovisceral manifestations. To evaluate clinical reports (5–9) and a case-control study (10) linking primary liver cancer with AIP and PCT, we conducted a population-based prospective study to evaluate cancer incidence and specific causes of death among hospitalized patients with porphyria by using linked registry data from Denmark and Sweden.

MATERIALS AND METHODS

The methods we used have been reported previously (11–13); a brief summary follows. Patients who were hospitalized for porphyria in Denmark during 1977–1989 (with Danish *International Classification of Diseases*, Eighth Revision discharge diagnosis codes 273.10–273.16, 273.18, and 273.19) and in Sweden during 1965–1983 (with Swedish *International Classification of Diseases*, Seventh Revision discharge diagnosis codes 289.40 and 289.41

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Abbreviations: AIP, acute intermittent porphyria; PCT, porphyria cutanea tarda.

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and Eighth Revision codes 273.10, 273.11, and 273.18) were identified from the centralized Danish Hospital Discharge Register and the Swedish Inpatient Register. Individual hospitalization records were linked to the Danish and Swedish Population, Migration, Cancer, and Causes of Death Registers.

All patients who were hospitalized for PCT or AIP during 1977–1989 in Denmark and 1965–1983 in Sweden were identified as eligible for this investigation. A patient's first hospitalization during the study period was defined as the initial hospitalization, regardless of any earlier hospitalizations for these metabolic disorders before the study period began. The risk of cancer was assessed among 401 Danish patients (after excluding 8 who died during the initial hospitalization) and 650 Swedish patients (after excluding 92 hospitalization records with incomplete identification numbers, 8 records with inconsistent dates, and 15 patients who died during the initial hospitalization). Follow-up began subsequent to the first hospitalization that listed porphyria as a discharge diagnosis and continued until the date of the subject's death, emigration, the first cancer diagnosis for Sweden (but continuing through subsequent primary cancers if a subject had more than one primary cancer in Denmark), or the end of follow-up (December 31, 1993, for Denmark and December 31, 1989, for Sweden), whichever event occurred first. Person-years, deaths, and incident cancers that occurred within 12 months following initial hospitalization were excluded to minimize selection or detection bias. The mortality analysis was limited to those subjects whose initial hospitalization was for porphyria only, again to minimize selection bias.

The expected cancer incidence or mortality rate was calculated by multiplying the observed number of person-years by the national sex-, age- (in 5-year intervals), calendar-year-, and site-specific cancer or mortality rates for the respective country. Cancer incidence rates in Denmark were based on multiple primary cancers, but those in Sweden were based on first primary cancers only. Risks were compared among patients with PCT versus AIP by using a combined Swedish and Danish standardized incidence ratio and standardized mortality ratio to increase the precision of the risk estimates. The numbers of Swedish and Danish porphyria patients were totaled separately for each type of porphyria; each of these two figures was then divided by the sum of the expected number of each type of porphyria. The 95 percent confidence interval of the standardized incidence ratio or the standardized mortality ratio was calculated by assuming that the number of observed cancers or deaths followed a Poisson distribution

(14). The mortality analyses were also stratified according to whether PCT or AIP was the only diagnosis or whether it was accompanied by other conditions. To evaluate potential confounders for primary liver cancer, we evaluated the risks for this malignancy among PCT and AIP patients with and without concomitant diagnoses of alcoholism, liver cirrhosis, or both. Patients who had other types of porphyria were not included in the analyses. Diagnosis of these types of porphyria may be less accurate than diagnosis of PCT and AIP, and there were very few ($n = 21$) of these patients in Sweden and only 25 percent ($n = 103$) of the total in Denmark.

RESULTS

Cancer incidence

There were fewer subjects with AIP than with PCT. On average, AIP patients were younger and were characterized by fewer incident cancers and deaths (table 1). Overall, small and significantly increased risks were observed for all cancers combined among PCT and AIP patients (table 2), and the risks did not differ substantially by calendar-year period or by interval between first hospitalization and cancer diagnosis. There was a more than 70-fold increase in primary liver cancer among AIP patients and a more than 20-fold increase among PCT patients. All but one of the patients with primary liver cancer had hepatocellular carcinoma that was diagnosed histologically. The mean number of years between initial hospitalization for PCT and a diagnosis of liver cancer was 4.8 and 4.5 in Denmark and Sweden, respectively. The interval between initial hospitalization for AIP and a diagnosis of liver cancer was 9.5 years in Sweden (no liver cancers were diagnosed among Danish patients with AIP). Liver cancer risks were notably elevated among porphyria patients, none of whom had a diagnosis of cirrhosis or alcoholism during any of their hospital visits. Lung cancer was increased about threefold among patients with both types of porphyria.

Mortality

For both forms of porphyria, total mortality and deaths due to malignancy were elevated among those who were discharged with a sole diagnosis of porphyria at initial hospitalization (table 3). PCT patients also had significantly elevated mortality rates from chronic obstructive pulmonary disease and cirrhosis of the liver. For PCT patients, no deaths were ascribed to porphyria in Sweden and only one in Denmark, whereas for nine AIP patients in Sweden and none in Denmark, porphyria was designated as the cause of death.

TABLE 1. Characteristics of Swedish (1965–1983) and Danish (1977–1989) patients by type of porphyria

Characteristic	Porphyria cutanea tarda*		Acute intermittent porphyria*	
	Sweden	Denmark	Sweden	Denmark
Cancer incidence†				
No. of patients	317	213	231	65
No. of males	213	118	82	21
Calendar year at entry (median)	1,978	1,983	1,977	1,982
No. of years of follow-up (median)	9	7	11	9
Total no. of person-years at risk‡	2,841	1,106	2,587	433
No. of incident cancer cases	36	20	14	5
Age at diagnosis in years (median)	70	65	61	52
Mortality, total porphyria				
No. of patients§	334	213	241	65
No. of males	225	118	85	21
No. of years of follow-up (median)	9	7	11	9
No. of deaths	135	58	52	11
Age at death in years (median)	71	67	62	67
Mortality, porphyria only¶				
No. of patients	191	154	99	21
No. of males	121	85	36	8
No. of years of follow-up (median)	10	7	14	9
No. of deaths	55	38	12	1

* Results are for first cancers only in Sweden, multiple primary cancers in Denmark.

† Total porphyria = 569 (300 males) patients in Sweden, 381 (182 males) patients in Denmark, excluding incident cancers, deaths, and emigrants within 12 months after initial hospitalization.

‡ Excludes person-years within the first 12 months after initial hospitalization.

§ More Swedish patients were included in the mortality than in the cancer incidence analyses because prevalent and incident cancers within the first 12 months were included.

¶ Includes patients whose sole diagnosis was porphyria at initial hospitalization.

TABLE 2. Standardized incidence ratios (SIR) and 95% confidence intervals (CI) for selected primary cancers in Sweden (first primary cancers during 1965–1989) and Denmark (multiple primary cancers during 1977–1993) combined* by type of porphyria†

Cancer site (ICD-7‡ codes)	Porphyria cutanea tarda (n = 530)				Acute intermittent porphyria (n = 296)			
	Sweden (no. observed)	Denmark (no. observed)	Combined SIR	Combined 95% CI	Sweden (no. observed)	Denmark (no. observed)	Combined SIR	Combined 95% CI
All cancers (140–209)	36	20	1.7	1.3–2.2	14	5	1.8	1.1–2.8
Oral/pharyngeal (140–148)	1	1	2.5	0.3–8.9	1	0	5.3	0.1–29.3
Stomach (151)	3	0	1.9	0.4–5.5	0	0	0.0	0.0–19.4
Colon (153)	2	1	1.2	0.2–3.5	1	0	1.5	0.0–18.6
Primary liver (155.0)	5§	2§	21.2	8.5–43.7	5§	0	70.4	22.7–164.3
Lung (162)	3	8	2.9	1.5–5.2	1	1	2.8	0.3–10.2
Breast (170)	2	0	0.8	0.1–3.0	2	1	1.4	0.3–4.2
Prostate (177)	4	0	0.8	0.2–2.1	0	0	0.0	0.0–7.0
Kidney (180)	2	0	1.8	0.2–6.6	0	1	3.2	0.1–18.0
Bladder (181)	3	1	1.8	0.5–4.7	0	0	0.0	0.0–9.7
All hematolymphoproliferative (200–209)¶	0	4	1.7	0.5–4.5	0	1	1.5	0.0–8.3

* Cancer sites shown are those for which three or more cancers occurred among the combined Swedish and Danish cohorts of porphyria cutanea tarda (PCT) plus acute intermittent porphyria (AIP). Cancers not shown for PCT patients include two esophagus, two rectum, two pancreas, one nonmelanoma skin, one cervix, one brain, one endocrine, and one not-otherwise-specified (Sweden); one bile duct, one larynx, and one nonmelanoma skin (Denmark). Cancers not shown for AIP patients include one secondary liver, one cervix, one endocrine, and one not-otherwise-specified (Sweden); one melanoma skin (Denmark).

† Excluding cancers first diagnosed within 12 months after initial hospitalization.

‡ ICD-7, *International Classification of Diseases*, Seventh Revision.

§ All primary liver cancers among Swedish patients (five in those with PCT and five in those with AIP) and Danish patients were hepatocellular cancer.

¶ The four hematolymphoproliferative malignancies in Danish patients with PCT included two non-Hodgkin's lymphoma and two multiple myeloma; the one hematolymphoproliferative malignancy in a Danish patient with AIP was acute nonlymphocytic leukemia.

TABLE 3. Standardized mortality ratios (SMR) and 95% confidence intervals (CI) for selected medical conditions in Sweden (1965–1989) and Denmark (1977–1993) combined, by type of porphyria, among those discharged with a diagnosis of porphyria only at initial hospitalization for porphyria*

Cause of death (ICD-8† codes)	Porphyria cutanea tarda (n = 345)				Acute intermittent porphyria (n = 120)			
	Sweden (no. observed)	Denmark (no. observed)	Combined SMR	Combined 95% CI	Sweden (no. observed)	Denmark (no. observed)	Combined SMR	Combined 95% CI
All causes (000–999)‡	55	38	1.5	1.2–1.9	12	1	1.9	1.0–3.3
All malignancies (140–207)	14	19	2.1	1.4–2.9	4	0	2.0	0.5–5.2
Diabetes mellitus (250)	2	0	2.4	0.3–8.7	0	0	0.0	0.0–38.7
Alcoholism (303)	1	0	5.9	0.1–32.8	0	0	0.0	0.0–53.6
Circulatory disease (390–458)	27	8	1.1	0.8–1.6	4	0	1.5	0.4–3.8
Ischemic heart disease (410–414)	15	5	1.0	0.6–1.5	3	0	1.7	0.4–5.1
"Other" heart disease (420–429)	5	0	2.2	0.7–5.1	0	0	0.0	0.0–16.6
Cerebrovascular disease (430–438)	4	1	0.9	0.3–2.2	1	0	2.0	0.1–11.1
Pneumonia (480–486)	0	1	0.6	0.0–3.2	0	0	0.0	0.0–21.8
Chronic obstructive pulmonary disease (490–493)§	4	2	3.1	1.1–6.7	0	0	0.0	0.0–32.1
Cirrhosis of the liver (571)	2	4	8.4	3.1–18.4	0	0	0.0	0.0–32.8
External causes (800–999)	2	0	0.7	0.1–2.5	1	1	2.5	0.3–9.1

* Excluding deaths within the first 12 months after initial hospitalization.

† ICD-8, *International Classification of Diseases*, Eighth Revision.

‡ Excludes porphyria as a cause of death; there was one death from porphyria among patients with porphyria cutanea tarda (PCT) and nine deaths from porphyria among patients with acute intermittent porphyria (AIP).

§ Includes bronchitis (five patients with PCT, no patients with AIP), emphysema (one patient with PCT, no patients with AIP), and asthma (no deaths).

DISCUSSION

The notable excesses of liver cancer in our follow-up study of PCT and AIP patients are consistent with clinical observations (15–20). Prior studies have suggested that risk increases with the duration of symptoms (21), although the mean intervals of 4–5 (PCT) and 9.5 (AIP) years between initial hospitalization and liver cancer diagnosis in our study are probably underestimates, since porphyria may have been diagnosed during earlier hospital admissions that were not included in the registry or during outpatient visits. Although PCT especially may be exacerbated by alcohol intake, the liver cancer risks (ranging from 1.5 to 4.2) associated with heavy alcohol consumption (22–24) are substantially lower than those we observed among the PCT and AIP cohorts. Hepatitis C infection also has been implicated in the relation between PCT and liver cancer (25, 26) and may have contributed to the excess mortality from cirrhosis of the liver in our study, although clinical reports indicate that a high alcohol consumption or cirrhosis can precipitate latent PCT (27, 28). The high risk of liver disease in porphyria patients also may be influenced by genetic factors (e.g., a mutation, Cys282Tyr, in one or both copies of a gene associated with hemochromatosis, which is independently associated with a high risk of primary liver cancer) or a variety of exposures, including alcohol, estrogens, aflatoxin, and chlorinated hydrocarbons (1–3, 9, 10, 29–36). While our prospective study

design implies that porphyria preceded the onset of primary liver cancer, the excess of this neoplasm in some families with AIP suggests that porphyrins or their precursors may affect the development of this neoplasm through cytochrome P450 or other metabolizing enzymes (10, 37–39).

The increases in mortality from lung cancer and chronic obstructive pulmonary disease among PCT patients suggests the possible role of cigarette smoking (which is highly correlated with alcohol consumption (40–42)), although the incidence of all types of smoking-related cancer was not consistently elevated in our study. However, cigarette smoking cannot explain the threefold increase in lung cancer risk that we observed, unless virtually all of the cohort members smoked (40–43). The reasoning behind this statement requires the assumption of an appropriate risk of lung cancer in smokers (a reasonable estimate might be a 10-fold increase), a prevalence of smoking in the population (PS), and a multiplier for porphyria (MP). Thus, the relative risk (RR) of lung cancer would be given by $RR = MP(10 - 1)PS + 1/(10 - 1)PS + 1$. Solving for $MP = 3 + 2/9PS$, if the prevalence of smoking in the population is only 10 percent, then porphyria patients would have to smoke more than five times as many cigarettes as the population (namely, 50 percent) to achieve a threefold increased risk of lung cancer. If the population prevalence of smoking is 25 percent, then the prevalence of smoking among porphyria patients must be nearly 100 percent. In fact, the highest popu-

lation prevalence of smoking that can be accommodated by this equation is 30 percent, with a corresponding prevalence of smoking among porphyria patients of 100 percent, to achieve a nearly threefold risk of lung cancer. Data from population-based surveys in Sweden estimated the prevalence of smoking to be 35 percent among men and 28 percent among women in 1980 (43). Therefore, even if all male and female porphyria patients smoked, a threefold lung cancer risk could not be explained solely on the basis of smoking. Porphyrins may enhance susceptibility to tobacco-related cancers, since experimental evidence has shown that induction of CYP1A2 (a cytochrome P450 enzyme that can be induced by cigarette smoke) contributes to the development of PCT (44–45).

Limitations of our study include not only the small numbers of patients but also the lack of information about hospitalizations prior to the registration period, results of laboratory tests and molecular studies, familial/genetic factors, treatment, smoking and drinking habits, and other confounding factors. If patients who are hospitalized for porphyria truly smoke more than persons in the general population, the higher prevalence of smoking among these patients could explain part but not all of the threefold excess. The diagnosis of porphyria may have been difficult particularly early in the study period, when diagnostic methods were not optimal; therefore, some misclassification may have occurred. In general, if true nondifferential misclassification is not corrected, any excess risks observed would tend to be reduced. For an indeterminate proportion of patients, the diagnosis of porphyria may already have been known for years at the time of initial hospitalization. Since the study focused on hospitalized patients, less severe cases treated as outpatients and those with latent porphyria would not have been included, whereas comorbidity may have increased the likelihood of being hospitalized. Patients with more serious forms of porphyria or with the combination of porphyria and comorbidity from complications of alcoholism or heavy cigarette smoking are most likely to be at increased risk for liver or lung cancer as well as for liver cirrhosis or chronic obstructive pulmonary disease, respectively. Important related conditions such as alcoholism and liver cirrhosis are underreported as patient diagnoses in medical records and thus may have been responsible for some of the excess risk of liver cancer that we observed. By restricting the mortality analyses to those persons who were discharged with the sole diagnosis of porphyria or by excluding person-years and deaths (and cancers in the incidence analyses) within the first 12 months after initial hospitalization for porphyria, we attempted to minimize biases resulting from increased medical surveillance, detection, and selection.

In summary, this population-based cohort investigation enabled us to quantify a very high incidence of primary liver cancer following PCT and AIP, as well as an excess mortality from liver cirrhosis among PCT patients, consistent with prior clinical surveys. If the modest excesses of lung cancer incidence and chronic obstructive pulmonary disease mortality are confirmed, further studies will be needed to clarify the role of cigarette smoking and susceptibility mechanisms that may be involved.

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